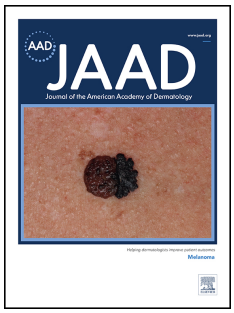
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Psoriasis and COVID-19: A bidirectional Mendelian randomization study

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Psoriasis and COVID-19: A bidirectional Mendelian randomization study

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There is a bidirectional link between psoriasis and infection; certain infections could trigger psoriasis and psoriasis is associated with an increased risk of serious infection (1). Currently, there is limited evidence on the association between psoriasis and COVID-19 (2). In a recent Mendelian randomization (MR) study in the Journal of American Association of Dermatology (JAAD), Xiaoyu Gu et al. suggested that genetic predisposition to psoriasis was associated with increased susceptibility to COVID-19 (3). Here, we conducted an updated MR analysis (Figure 1) including genome-wide summary statistics for psoriasis with a larger sample size and doctor-diagnosis of psoriasis, the latest release of COVID-19 genome-wide association study (GWAS) and several sensitivity analyses to examine the MR assumptions.

Summary statistics for psoriasis were obtained from the largest GWAS meta-analysis of European ancestry, with cases defined as dermatologist-diagnosed psoriasis with 13,229 cases and 21,543 controls (after excluding the 23andMe cohort) (4) (eTable 1; available via Mendeley at data.mendeley.com/drafts/hff49h4zpn). For COVID-19, the latest available data (round 7) from the COVID-19 Host Genetics Initiative were gathered (www.covid19hg.org/results/r7/) incorporating in the analysis all the available phenotypes (5). The inverse variance weighted (IVW) method was used as the primary method and sensitivity analyses were conducted including weighted median, MR-Egger, MR-PRESSO, and weighted mode. A Bonferroni corrected significance level $p < .05/3$ (=0.017) was considered statistically significant and MR analysis was performed with R version 4.1.2 using the "TwoSampleMR" and "MRPRESSO" packages.

The MR analysis did not find any association between genetical predisposition to psoriasis with increased susceptibility to COVID-19 (COVID-19 vs population; $OR_{IVW} = 0.994$; 95% CI 0.98 to 1.009; $p = 0.465$); (COVID-19 hospitalised vs population; $OR_{IVW} = 1.003$; 95% CI

0.965 to 1.043; $p = 0.876$); and (COVID-19 severe vs population; $OR_{IVW} = 1.009$; 95% CI 0.951 to 1.07; $p = 0.764$) in accordance with the sensitivity analyses (Table 1). There was little evidence for horizontal pleiotropy (MR-Egger intercept $p = 0.499$, $p = 0.106$, & $p = 0.106$). Effect estimates for the association between exposure and outcome are in eTable 2 (available via Mendeley at data.mendeley.com/drafts/hff49h4zpn). Even after correcting for outliers, the MR-PRESSO did not show any association with any COVID-19 phenotype (Table 1) and the leave-one-SNP out analysis did not reveal any influential SNP (eTable 3 & 4; available via Mendeley at data.mendeley.com/drafts/hff49h4zpn). When we evaluated the bidirectional association, genetic predisposition to COVID-19 did not elevate the risk of developing psoriasis (Table 1).

Our results do not support the previous study conducted by Xiaoyu Gu et al. (3). There are several reasons for this discrepancy. Firstly, the GWAS of psoriasis by the Neale laboratory, which Xiaoyu Gu et al used, had a limited sample size (3,871 vs 13,229 included here) and was proven to misclassification due to the self-reported diagnosis of psoriasis. Secondly, Xiaoyu Gu et al. (3) did not take advantage of the latest available data for COVID-19 during their analysis (round 6, release date: June 15, 2021) which included a substantially higher number of cases. Most importantly, the phenotype used by Xiaoyu Gu et al was just "COVID-19 vs population" in comparison to the more robust phenotype of "COVID-19 hospitalised vs population" and "COVID-19 severe vs population" used in our analyses. We have also confirmed our findings with several sensitivity analyses none of which suggested a causal association between psoriasis and the severity of COVID-19 disease. In conclusion, our study does not support that genetic predisposition to psoriasis is associated with higher susceptibility to being infected, hospitalised, or developing severe COVID-19 in Europeans.

AUTHOR CONTRIBUTION

C.V.C had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: C.V.C. Acquisition, and statistical analysis of the data: C.V.C. Drafting of the manuscript: C.V.C. Critical revision of the manuscript for important intellectual content: C.V.C, K.K.T, I.T. All authors accepted the final version.

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REFERENCES

1. Rademaker M, Agnew K, Anagnostou N, Andrews M, Armour K, Baker C, et al. Psoriasis and infection. A clinical practice narrative. Australas J Dermatol. 2019;60(2):91–8.
2. Psoriasis association. COVID-19 Information. 2022. Available at: https://www.psoriasis-association.org.uk/psoriasis-and-treatments/covid-19-information.
3. Gu X, Chen X, Shen M. Association of psoriasis with risk of COVID-19: A 2-sample Mendelian randomization study. J Am Acad Dermatol. 2022;5–6.
4. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun. 2017;8(May):1–8.
5. Ganna A, Unit TG, General M. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the

124 SARS-CoV-2 virus pandemic. Eur J Hum Genet. 2020;28(6):715–8.

125

126 **Table 1.** Association of genetically predicted psoriasis with susceptibility to COVID-19.

Exposure	Outcome	N SNPs	MR-method	OR (95%CI)	p-value
Psoriasis	COVID-19 (Covid vs. population)	43	IVW	0.994 (0.98-1.009)	0.465
			Weighted median	0.994 (0.98-1.008)	0.397
			Egger slope	1.002 (0.976-1.028)	0.881
			Weighted mode	0.981 (0.958-1.004)	0.119
			PRESSO	0.994 (0.985-1.004)	0.296
			Egger intercept	-	0.499
Psoriasis	COVID-19 (Hospitalised vs. population)	43	IVW	1.003 (0.965-1.043)	0.876
			Weighted median	1.000 (0.968-1.034)	0.979
			Egger slope	1.051 (0.982-1.124)	0.155
			Weighted mode	1.005 (0.953-1.06)	0.843
			PRESSO	0.99 (0.965-1.016)	0.448
			Egger intercept	-	0.106
Psoriasis	COVID-19 (Severe vs. population)	43	IVW	1.009 (0.951-1.07)	0.764
			Weighted median	0.992 (0.954-1.033)	0.716
			Egger slope	1.082 (0.978-1.197)	0.134
			Weighted mode	0.987 (0.944-1.033)	0.582
			PRESSO	0.988 (0.959-1.016)	0.423
			Egger intercept	-	0.107
COVID-19 (Covid vs population)	Psoriasis	14	IVW	0.919 (0.321-2.631)	0.875
			Weighted median	1.206 (0.91-1.598)	0.191
			Egger slope	2.284 (0.346-15.06)	0.408
			Weighted mode	1.255 (0.942-1.671)	0.144
			PRESSO	1.25 (1.065-1.467)	0.018
			Egger intercept	-	0.279
COVID-19 (Hospitalised vs population)	Psoriasis	30	IVW	1.103 (0.781-1.558)	0.578
			Weighted median	1.038 (0.928-1.162)	0.512
			Egger slope	0.946 (0.509-1.758)	0.861
			Weighted mode	1.042 (0.93-1.168)	0.479
			PRESSO	1.067 (0.956-1.017)	0.259
			Egger intercept	-	0.561
COVID-19 (Severe vs population)	Psoriasis	26	IVW	0.931 (0.762-1.138)	0.488
			Weighted median	1.023 (0.95-1.102)	0.542
			Egger slope	1.058 (0.749-1.495)	0.751
			Weighted mode	1.024 (0.954-1.099)	0.518
			PRESSO	1.024 (0.955-1.099)	0.507
			Egger intercept	-	0.381

127

FIGURE LEGEND

Figure 1. Study design overview and assumptions of the MR design. Dashed lines represent potential pleiotropic or direct causal effects between variables that would violate Mendelian randomization assumptions. Assumption 1: Genetic variants are associated with the exposure; Assumption 2: Genetic variants are not associated with any confounders; and Assumption 3: Genetic variants influence risk only through the exposure and not through any alternative pathways. The MR design can reduce residual confounding and reverse causality, thereby reinforcing the causal inference of an exposure-outcome association. The basis of this is that genetic variants, selected as instrumental variables for studying the effect of modifying the exposure, are randomly allocated at conception and are therefore less vulnerable to confounding from environmental factors and reverse causation.